Aus dem Laboratorium für Pädiatrische Klinische Chemie
und Lipidforschung (Leiterin: Prof. Dr. I. R. Kupke)
am Institut für Klinische Chemie und Laboratoriumsdiagnostik
(Direktor: Prof. Dr. W. Rick) und aus der Kinderklinik A
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der Medizinischen Einrichtungen der Unversität Düsseldorf

RISK INDICATORS OF ATHEROGENESIS IN GERMAN AND JAPANES CHILDREN IN DÜSSELDORF

Dissertation
zur Erlangung des Grades eines Doktors der Medizin
der Medizinischen Fakultät der Universität Düsseldorf

vorgelegt von

Friedrich-Wilhelm Wellern

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RISK INDICATORS OF ATHEROGENESIS IN GERMAN AND JAPANESE CHILDREN IN DUESSELDORF [1)]

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Summary - A number of variables related to the risk of atherogenesis were studied in a group of German and Japanese children (3-7 years) living in Duesseldorf. Height, weight, blood pressure and various constituents of capillary blood serum were measured (glucose (GLUC), uric acid (UA), total, free and esterified cholesterol (TC, C, CE), triacylglycerols (TG), phosphatidylethanolamine (PE), phosphatidylcholine (PC), α-, pre-β - and β-lipoprotein cholesterol (α-, pre-β-, β-LP). New micromethods used in this study offer the advantage of analyzing the lipids and LP cholesterol in a total of only 31 μl capillary blood serum.

Among 79 Japanese children, 78 (49 boys and 29 girls) had normal age-related height and weight; the same applied to 335 out of 380 German children (172 boys and 163 girls). Data of these normally grown children of both races served for comparison.

Japanese children were smaller than German children, but they had nearly the same weight. Systolic and diastolic blood pressure was higher in Japanese than in German children. German boys were taller and heavier than German girls, a difference not observed in the Japanese group.

Japanese children had markedly lower levels of TC, CE and pre-β-LP than German children (6.3/7.0/40%, respectively, $p<0.0005$). These results might be related to the typical Japanese diet relatively low in cholesterol, high in its ratio of polyunsaturated/saturated fatty acids, and rich in fish and soy products. Furthermore, higher levels of PE (8.0%, $p<0.0005$) but lower levels of PC (4.4%, $p<0.01$) were observed in Japanese compared to German children; a relative deficiency of methionine is discussed as a putative

causal factor.

In the German group, boys had higher GLUC levels than girls (5.5%, $p<0.0005$), whereas TG levels were higher in girls than in boys (10%, $p<0.01$), as also tended to be the case for TC levels (3.5%, $p<0.10$). This is reflected in significantly higher levels of C (6.7%, $p<0.01$) and β-LP (8.7%, $p<0.0005$) for the girls. In the Japanese group, girls also showed a tendency toward higher levels of TC (5.5%, not significant), C and β-LP (5.1/10%, respectively, $p<0.10$).

The following conclusions may be drawn: 1. The entire procedure used in this study has again proved to be highly suitable for the examination of large groups of children outside the clinic. 2. In both races, several metabolic parameters were dependent on sex, even at this young age. 3. The difference between the German and Japanese children suggest that environmental influences, especially dietary influences, may be more important than racial influences. 4. Relatively high levels of CE and pre-β-LP in German children, but lower levels of these lipids in Japanese children also appear to be related either to the German or Japanese type of diet. It is tempting to speculate that these different levels of CE and pre-β-LP might have some relation to the differential risk of CHD in German and Japanese people.

VAKG. LEIDEN

INTRODUCTION

In major industrial countries such as the United States and the Federal Republic of Germany, cardiovascular diseases still lead malignant tumors as a cause of death; by far the majority of these deaths are ascribable to coronary heart disease (CHD), followed by cerebrovascular disease (CVD) (35, 53, 58). This contrasts with the situation in Japan, where CVD ranks first and CHD third, after malignancy (13). Nevertheless, CHD mortality in Japan has nearly trebled in the past 20 years, with CVD mortality remaining about constant (22).

Numerous autopsy studies have demonstrated that the roots of atherosclerosis reach back into infancy and childhood (40, 43, 60, 65). Prior to its clinical manifestation the atherosclerotic process may progress cryptically for several decades. Therefore, efforts toward prevention of the disease and intervention in the atherosclerotic process ought to begin as early in life as possible (14, 19, 33, 37, 67). Such efforts constitute one possible means of achieving a significant reduction in the high mortality and morbidity of the disease (5).

Numerous epidemiologic studies have shown that the plasma levels of several lipids and lipoproteins play a key role in the pathogenesis of atherosclerosis (7, 9, 20, 41, 68). Other risk factors that have been reported include sex-linked influences as well as ethnic and in particular environmental influences, for example nutrition, socio-economic structures, etc. (49). Thus, it has been pointed out that ethnic groups that have emigrated to another country adapt their style of life to their new environment, which is not without an effect

on their metabolism: The adoption of a Western life-style by Japanese men living in Hawaii and California (38, 39, 69) or by Greenlandic Eskimos living in Denmark (2) has been reported to shift the metabolic patterns of lipids and lipoproteins towards those of the local populations, whose patterns are associated with increased risk of CHD. Correspondingly, in subjects from Western countries living in Japan and adjusting to a Japanese life-style, the metabolic patterns shift towards those of the native population (70). Obviously, environmental changes are tending to equalize racial differences.

Such observations formed the starting point of the question pursued in the present study, namely, whether Japanese children who had been living for several years in Duesseldorf differ with respect to various metabolic parameters from their German peers.

During 1977/78, we already made a study of 566 German children (3 - 7 yr) in 17 kindergartens in Duesseldorf, in which the following metabolic parameters were investigated (25, 27): Glucose (GLUC), uric acid (UA), total, free and esterified cholesterol (TC,C,CE), triacylglycerols (TG), phosphatidylethanolamine (PE), phosphatidylcholine (PC), α-, pre-β - and β-lipoprotein cholesterol (α-, pre-β-, β-LP). By using newly developed micromethods (28, 29) it was possible to determine the lipids and lipoproteins in only 31 μl of capillary serum. The study itself was conceived as a field study; the methods applied proved to be gratifyingly appropriate for the examination of such young children outside the clinic.

We have now applied these same methods to the examination of 79 Japanese children (3 - 7 yr) from families in middle and upper

management in Duesseldorf. It was our goal, by comparing the results with those on the German children, to achieve some insight into the effects of race, sex and environment on metabolism. The present results will also be discussed with regard to a differential disposition for the risk of atherosclerosis.

SUBJECTS AND METHODS

Subjects, Anthropometric measurements and Blood Sampling Procedure

From October, 1979, to February, 1980, 79 Japanese children (3 - 7 yr) in 12 kindergartens in Duesseldorf were examined (26). These children belonged to families of the middle and upper industrial management. The average residence time of these 79 children in Duesseldorf was 23 $\pm$ 13.5 months (6 - 67 months), with the mode of the frequency distribution located at 12 months. The younger children may go to the Misono-en kindergarten, which is reserved for Japanese children, but most children go to German kindergartens together with German children.

From an inquiry among mothers of the Japanese children we know that Japanese people in Duesseldorf have been adapting to the German life-style, including a change in their eating habits: Japanese families in Duesseldorf consume more food rich in animal protein and fat (i.e. beef and pork) and dairy products (i.e. butter, cheese, yoghurt etc.) than families in Japan. On the other hand, typical Japanese foods like fish, rice and soy products are consumed to a lesser degree than in Japan, if only because they are relatively expensive in Duesseldorf.

Provided permission was given by the head nurses, written

information in Japanese on the content and goals of the examination was given to nurses and parents at least one week beforehand. It was clearly pointed out that the examination would be performed on a voluntary basis, that it would be free of charge, and that only those children whose parents had given written consent would be examined. About 95% of the children participated in the examination, and numerous parents and nurses asked to be examined, too. The results were made available - again by a letter in Japanese - to the parents via the head nurses. In 3 cases of pathologic results (moderate hypercholesterolemia) the parents were advised to consult their pediatrician.

The examination took place in the kindergartens between 8 and 9 A.M. . The children had fasted for at least 12 hours and remained seated during the blood pressure measurements and the blood sampling procedure. First, height and weight, without shoes and jackets on, were measured. Then systolic and diastolic blood pressure were determined as follows : Before the measurements, the children remained in the sitting position for at least 5 minutes. The systolic and diastolic blood pressure (1st and 4th Korotkoff phases) were determined using a standard mercury device with a small cuff for children (width 10 cm, length 19 cm). This method approaches respective recommendations (50,67). Following hyperemization, 0.5 - 1 ml of capillary blood could easily be collected by lancing the finger tip. The whole procedure is described elsewhere in detail (25, 31).

Definition of Groups

In order to exclude children whose anthropometric data ranged

beyond the normal limits for this age group (< 3rd and > 97th percentile), height and weight of each child were compared to Japanese growth tables (61). Thus, one girl, exhibiting overweight, was excluded. The remaining 78 children, 49 boys and 29 girls, had normal age-related height and weight and were accepted as being anthropometrically "normal".

Data on a group of 335 German children (3 - 7yr) have been reported in a previous study (25, 27). For the purposes of the present study, these data were averaged for boys (n = 172) and girls (n = 163) and served as reference data for the German group. In order for the results to be as nearly comparable as possible, the Japanese children were examined under the same conditions, i.e. season of the year (winter), time of day and blood sampling procedure etc. . Analytical methods, used in both groups, were identical.

Preparation and Storage of Serum Samples

After clotting at room temperature, the blood was centrifuged at 3000 rpm for at least 10 min. within 1 - 2 hours. The serum was stabilized by adding 1 µl of a dipotassium-ethylene-diamine-tetraacetate (EDTA) - solution (5%, pH 7) to 100 µl serum.

The serum samples were stored at +4°C and analyzed on the same or next day. High-performance thin-layer chromatography (HPTLC , see below) of the lipids was carried out later. Since the small sample volumes had to be protected against evaporation, approximately 50 µl of serum was transferred immediately into a capillary tube which was sealed at each end with stretched elastic laboratory

film (Parafilm "M", American Can Company, Dixie/Marathon, Greenwich, CT, 06830). The serum was frozen immediately and stored at -20°C.

Analytical Methods

For GLUC analysis serum was deproteinized immediately. GLUC and UA were determined enzymatically using test combinations (Boehringer, Mannheim, F.R.G.).

A microelectrophoresis system was used for phenotyping the lipoprotein patterns (Corning-EEL/IMA, Gießen, F.R.G.).
The lipid profiles (CE, C, TG, PC, PE) were analyzed by high-performance thin-layer chromatography (28). After direct application of 0.5 µl capillary serum to the silica-gel layer, the lipids were separated and quantitated by fluorescence measurement. The coefficients of variation (CV) were $< 2.8\%$ for all lipids tested, and recovery of known amounts of lipids was 96 - 100%. Data obtained by current methods and by HPTLC were closely correlated.

For the determination of LP-cholesterol without ultracentrifugation, the LP-fractions of 15 µl capillary serum were separated by electrophoresis on agarose-gel (29). The samples were dried, dissolved in HCL and neutralized with a saturated Tris solution producing a Tris buffer system at pH 7. This system was found to be highly suitable for enzymatic determination of LP-cholesterol. The kinetic properties and linear range of this reaction system, the precision (CV 1 - 3%) and recovery of TC (100%) were found to be optimal. This microprocedure gave results nearly identical to those obtained with ultracentrifugation (30).

Statistical Methods

Groups were compared by means of the non- parametric Mann-Whitney U-test. Pairs of variables were examined by linear regression analysis.

RESULTS

Anthropometric Criteria and Blood Pressure

Racial and Sex Differences

Table 1 includes data on age, height, weight and blood pressure. Several differences between the groups examined may be discerned: The Japanese children were slightly older than the German children (2 months), but they were shorter (8 cm) and weighed the same. They also had a higher systolic and diastolic blood pressure than the German children (102/73 and 94/60 mmHg). The German and Japanese groups taken as a whole, did not differ with respect to weight. However, German boys were 1 month younger but significantly heavier than Japanese boys (1.2 kg).

The German boys were taller and heavier than the German girls (4 cm / 1.1 kg), and also had a higher systolic blood pressure (96 vs. 93 mmHg), whereas diastolic blood pressure was identical in both sexes. In contrast, the Japanese girls had higher systolic and diastolic blood pressure than the Japanese boys (105/78 and 100/70 mmHg).

Metabolic Patterns

1. Racial Differences

Table 2 contains data on concentrations of metabolic parameters,

determined in the capillary serum of the German and Japanese children, along with calculated data.

The concentrations of GLUC, UA, TG, C, α- and β-LP were nearly identical in both groups of children. The concentration of TC was significantly lower (6.3%) in Japanese children, which was reflected in significantly diminished CE and pre- β -LP concentrations (7.0/40%) (Fig. 1).

The differences in these parameters had a marked influence on the percent distribution of LP-cholesterol and on the corresponding ratios of these variables: The percentages of α- and β-LP were significantly higher, that of pre- β -LP was significantly lower in the Japanese than in the German group. The β:α -LP ratio was identical in both groups, while the ratios of CE:C, TC: β -LP and TC:α -LP were markedly lower in the Japanese children.

As a further comparison of the two groups taken as a whole, the Japanese children had higher levels of PE but lower levels of PC (8.0/4.4%) than the German children (Fig. 1). This caused significantly lower PC:PE and PC:α -LP ratios in the Japanese group.

We also compared children of the same sex but of different race (Table 5). There were no unequivocal differences in the concentrations of GLUC, UA, TG, C, α- and β-LP or in the β:α ratio between the two groups of boys. The same was true of the two groups of girls, with the exception of the concentration of GLUC, which was higher in the Japanese than in the German girls (3.4%). The concentrations of PC, PE and TC differed significantly between the two groups of boys, but the same tendency between the

groups of girls was not significant ($p < 0.10$). Perhaps this is due to the relatively small number of Japanese girls; in addition, the differences in the concentrations of these variables were also smaller. However, all other differences described above between the German and Japanese groups as a whole were reflected to the same extent in this comparison of boys and girls of different race.

2. Sex Differences

No dependence on sex appeared for the concentrations of UA, PC, PE, CE, α- and pre-β-LP in either racial group (Table 3,4). However, GLUC levels were markedly higher in German boys than in girls (5.5%), whereas the levels of TG were markedly higher in German girls than in boys (10.1%). This sex difference was not seen in the Japanese group. Furthermore, both the German and the Japanese girls tended to have higher levels of TC (3.5/5.5%), C (6.7/5.1%) and β-LP (8.7/10.1%) than did the boys.

In German girls, the percentage of β-LP was significantly higher, but that of α- and pre-β-LP significantly lower than in German boys. These differences were also found in the Japanese group, but they were smaller and statistically not significant.

Compared to the German girls, the German boys had markedly higher ratios of CE:C and TC:β-LP and lower ratios of TC:α-LP and β:α-LP, the ratios of PC:PE and PC:α-LP being nearly identical. The Japanese boys showed only slightly higher ratios of CE:C and TC:β-LP than girls, all the other ratios being nearly identical.

Correlation Analysis of Metabolite Pairs

Table 6 includes data obtained by correlation analysis. Of the 25 metabolite pairs tested, TC:C, TC:CE, CE:C, TC: β-LP closely correlated in all groups. Except in the Japanese girls, PC had a slight but significant correlation with several metabolites, whereas GLUC was not unequivocally associated with any of the other variables examined. Finally, TG showed a moderate positive association with pre-β-LP, but a moderate negative association with α-LP.

DISCUSSION

Anthropometric Criteria and Blood Pressure

Racial and Sex Differences

The anthropometric and blood pressure data for our German and Japanese children (Table 1) refer to groups selected on the basis of German and Japanese growth tables (61, 64) to range within the normal limits. Secondary influences related to retarded growth, tall growth and obesity were thus excluded.

Although Japanese school children are the tallest in Asia (18), the Japanese children in Duesseldorf were shorter than their German counterparts (107/115 cm), but they weighed the same (Table 1). Compared to American white boys and girls of the same age, German boys and girls were slightly taller (111/110 cm and 117/113 cm, respectively) but they weighed approximately the same. Sex differences in height and weight observed in the German children were not found among the Japanese children, nor were they reported for American children, either whites or blacks (3).

It should be mentioned that blood pressure measurements were not performed under strictly standardized conditions, but the method used was the same in both groups of children (Table 1). The blood pressure of our German children was nearly identical with the standards reported for American children of the same age (50). The blood pressure of the Japanese children, on the other hand, was higher. Interestingly, the systolic blood pressure of children (6 - 11 yr) from a North-Eastern district in Japan (52) has been reported to be even higher than that of the Japanese children in Duesseldorf (109 mmHg for boys and 110 mmHg for girls). The possible relation of this phenomenon as observed in young children to the risk of atherogenesis ought to be worth further study.

Metabolite Patterns

1. Sex Differences

Several sex differences were observed in the variables tested (Tables 3 and 4). Firstly, GLUC levels were significantly higher in German boys than girls, while no such difference was seen in the Japanese group. This phenomenon remains to be elucidated. Further, the levels of TG, C and β-LP were markedly higher in German girls than in boys, and TC was slightly higher in the girls. Since TG and TC in β-LP/LDL are related to each other (6), the augmented serum TG levels found in our German girls might reflect the corresponding high levels of β-LP, which in turn elevates the $\beta:\alpha$ -LP ration. This inherent factor should be considered when using the ratio as an " atherogenic index " (in Ref. 25). C and β-LP levels were also higher in the Japanese girls, but

this did not apply to the TG levels (Table 4). Note that comparable sex differences in the TG, TC and β-LP levels and in the ratios LDL:HDL (β : α-LP) and TC:HDL (TC: α-LP) are also found in most of the other pediatric populations reported in the literature (Table 7).

2. Racial Differences

Some interesting racial consistencies seem to exist. Thus, while C was the same in both groups, but CE as well as TC were markedly lower in the Japanese than in the German children (Table 2, Fig. 1), the proportion of CE was also the same (74%). This result is consistent with data reported for white and black neonates (73-75% (4)) and for another group of white children (1 - 7 yr : 73% (24)), suggesting that percentage CE may be independent of race.

A further consistency is found in the correlations of TC: β-LP and TC: α-LP. Thus, not only is there a close correlation of TC: β-LP in our German and Japanese children (r = 0.71/0.84) (Table 6), this is also consistent with data from the Bogalusa Heart Study (for white and black children (5 - 14 yr) : r = 0.75/0.73 (56)). Moreover, a weak but significant correlation of TC: α-LP in our German and Japanese children (r = 0.39/0.39) corresponds to data obtained on boys (7 - 8 yr) from 16 different countries (mean value (r) = 0.35 (23)) and on children from the Bogalusa Heart Study (for white and black children (5 - 14 yr): r = 0.44/0.60 (56)).

As mentioned above, TC levels in Japanese children were lower,

which is reflected on the one hand in reduced CE levels. On the other hand, low TC levels may also be viewed as the result of lowered pre-β-LP. This might be due to influences of the typical Japanese diet, relatively rich in fish and other sea food, as well as algae, rice, vegetables and soy products (1, 21). Roughly half of the protein and fat in this Japanese diet originates from animal sources (13), compared to about 70% in the diet of German children (4 - 7 yr) (59). Furthermore, the nutritional fat in the Japanese diet contains a relatively high proportion of polyunsaturated and a low proportion of saturated fatty acids (high P/S-ratio),as well as a relatively low proportion of cholesterol (57, 63). This type of diet has been reported to reduce serum TC levels in adults and children - even in different ethnic groups (10, 11, 34, 45, 54). Moreover, this diet was also seen to reduce very-low-density lipoprotein cholesterol (VLDL), while high-density and low-density lipoprotein cholesterol (HDL, LDL) were not affected (62). Thus, our result of lower TC and pre-β-LP levels in the Japanese children seems to be explicable on the basis of these data.

Furthermore, it is a truism that people living in foreign countries adapt to local influences. Thus, it has been observed that Japanese living in Hawaii and California are adapting to the American life-style, including eating habits (15, 63). Since the proportion of TC is higher and the P/S-ratio is lower in the American diet (57), higher TC levels (17 - 25%) in Japanese in Hawaii and California, compared to those living in Japan (46), may be plausible. Similarly, Japanese in Duesseldorf

are adapting to the German life-style, including eating habits (see chapter SUBJECTS AND METHODS). Nevertheless, the basic diet of the Japanese people in Duesseldorf is still typically Japanese. This "German-Japanese" type of diet might explain the observation that Japanese children in Duesseldorf had higher TC levels (about 12% (Table 7)) than children from the first grade of an elementary school in Tokyo (47), but markedly lower TC levels (6.3%) than our German children in Duesseldorf.

It has been observed that the consumption of soy products leads to reduced serum TC and pre-β-LP levels in healthy subjects, as well as in patients with lipid disorders (8, 16, 36, 55). Recent studies have demonstrated that a diet consisting mainly of fish (e.g. mackerel) can diminish the TC level by 7.5% and the pre-β-LP level by more than 50% (66). These studies show that serum TC and pre-β-LP levels can be reduced by a low-cholesterol diet with a high P/S-ratio, as well as by a diet, such as the Japanese one, which is rich in soy and fish products. Since such fare is still the basic diet of Japanese children living in Duesseldorf, low TC and pre-β-LP levels found in these children are not surprising.

VLDL-cholesterol concentrations have been reported to be positively correlated with cholesterol turnover (42), and VLDL relatively rich in cholesterol is regarded as having an inherent atherogenicity (12). This LP (pre-β-LP), together with poorly soluble serum-CE, was significantly higher in German than Japanese children. Accordingly, one might speculate that this metabolic difference may be related in some way to the differential risk

of CHD in German and Japanese people.

As a final point relating to diet, note that our Japanese children had significantly lower levels of PC and higher levels of PE than the German children, resulting in a lower PC:PE ratio (Table 2 and Fig. 1). Nevertheless, the degree of correlation between these metabolites was the same in both groups of children, as well as for girls and boys (Table 6). Since PC and PE are related to each other by transmethylation processes dependent on the availability of methionine (25, in Ref. 32), a relative deficiency of this amino acid in Japanese children might be the cause, also explicable by differences in German and Japanese diets; since in the latter total protein intake consists to a considerable extent of soy protein, which is relatively poor in methionine (17).

CONCLUDING REMARKS

The entire procedure in the kindergartens and the analysis of several metabolic parameters in capillary serum using new micromethods have again proved to be adequate for the screening of large pediatric populations, especially outside the clinic. Several metabolic parameters showed a dependence on sex, even at this young age. The differences between the German and Japanese groups suggest that environmental influences, in particular dietary ones, are more important than racial differences. It is generally accepted that high levels of TC and also pre-β-LP represent atherogenic factors. Since low levels of these metabolites found in Japanese children are likely to be related to a Japanese

type of diet, the latter might be recommended for dietary regimens in prevention and intervention strategies. This is in accordance with recommendations of an expert committee of the WHO (49).

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LEGENDS

TABLE 1

ANTHROPOMETRIC DATA AND BLOOD PRESSURE

Data are expressed as $\bar{x}$ = mean, S.D. = standard deviation, and selected percentiles; level of significance (U test) : p = between sexes, P = between races; N.S. = not significant.

TABLE 2

COMPARISON OF JAPANESE CHILDREN WITH GERMAN CHILDREN

For legend see Table 1.

TABLE 3

COMPARISON OF GERMAN BOYS WITH GERMAN GIRLS

For legend see Table 1.

TABLE 4

COMPARISON OF JAPANESE BOYS WITH JAPANESE GIRLS

For legend see Table 1. Since the number of boys and girls in the Japanese group was relatively small, only the 10th, 50th, and 90th percentiles are presented.

TABLE 5

COMPARISON OF CHILDREN OF THE SAME SEX AND DIFFERENT RACE

N.S. = not significant; vs = versus. Data indicate levels of significance (P) by U test. For basic data see Tables 3 and 4.

TABLE 6

CORRELATION ANALYSIS OF METABOLITE PAIRS IN JAPANESE AND GERMAN CHILDREN

Data : correlation coefficients; levels of significance :

a = $P < 0.0005$, b = $P < 0.0025$, c = $P < 0.005$, d = $P < 0.01$,

e = $P < 0.05$, f = $P < 0.10$.

TABLE 7

SYNOPSIS OF DATA REPORTED BY OTHER INVESTIGATORS

Data are expressed in mmol/l ($\bar{x} \pm$ S.D.). Data obtained on children in Duesseldorf were extrapolated for venous serum concentrations (31). High (HDL), very low (VLDL) and low (LDL) density lipoprotein cholesterol.

FIGURE 1

COMPARISON OF JAPANESE CHILDREN WITH GERMAN CHILDREN IN DUESSELDORF (MAIN RESULTS)

Data are expressed as $\bar{x} \pm$ S.D..

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TABLE 1

		German Children (n = 335)								Japanese Children (n = 78)								
				Percentiles								Percentiles						
		$\bar{x}$	S.D.	5	10	50	90	95	p	$\bar{x}$	S.D.	5	10	50	90	95	p	p
Age (yr)	Total	5.05	0.99	3.5	3.8	5.0	6.2	6.3		5.24	1.22	2.8	3.2	5.4	6.5	6.7		<0.025
	Boys	5.14	1.10	3.5	3.8	4.9	6.3	7.0	N.S.	5.21	1.25	2.9	3.2	5.4	6.5	6.6	N.S.	<0.025
	Girls	4.97	0.87	3.4	3.8	5.0	6.1	6.3		5.29	1.19	2.4	3.2	5.5	6.4	6.7		<0.025
Height (cm)	Total	115	7.4	100	102	113	122	124		107	8.5	88	94	107	117	119		<0.0005
	Boys	117	7.6	101	103	114	122	124	<0.025	107	8.8	87	93	107	117	119	N.S.	<0.0005
	Girls	113	7.3	99	101	112	120	124		107	8.2	87	94	107	115	118		<0.005
Weight (kg)	Total	18.9	3.0	14	15	16	22	23		18.1	2.8	13	14	18	21	22		N.S.
	Boys	19.3	3.0	14	15	19	22	24	<0.0025	18.1	2.8	13	14	17	21	22	N.S.	<0.01
	Girls	18.2	3.0	14	14	18	22	23		18.2	2.9	12	14	18	21	22		N.S.
Blood pressure (mm Hg)																		
(syst.)	Total	94	12	76	77	90	108	114		102	11	80	83	96	115	118		<0.0005
	Boys	96	13	75	77	94	109	116	<0.025	100	10	80	82	94	109	114	<0.025	<0.025
	Girls	93	11	71	74	89	107	110		105	12	82	90	98	118	125		<0.0005
(diast.)	Total	60	9	45	46	59	69	76		73	11	50	57	69	82	89		<0.0005
	Boys	60	9	45	47	57	70	77	N.S.	70	10	50	55	68	79	84	<0.0025	<0.0005
	Girls	60	9	45	46	57	69	75		78	9	60	65	74	85	89		<0.0005

TABLE 2

Variable	German Children (n = 335)							Japanese Children (n = 78)							P
			Percentiles							Percentiles					
	$\bar{x}$	S.D.	5	10	50	90	95	$\bar{x}$	S.D.	5	10	50	90	95	
Concentration (mmol/l)															
G L U C	5.19	0.59	4.06	4.50	5.06	5.88	6.33	5.22	0.44	4.43	4.59	5.18	5.77	5.81	N.S.
U A	0.218	0.053	0.130	0.150	0.215	0.280	0.310	0.216	0.038	0.142	0.161	0.212	0.257	0.269	N.S.
T G	0.83	0.32	0.32	0.44	0.83	1.22	1.40	0.82	0.27	0.45	0.52	0.76	1.13	1.30	N.S.
P C	2.35	0.36	1.75	1.90	2.33	2.84	2.96	2.25	0.30	1.80	1.85	2.19	2.68	2.71	<0.01
P E	0.50	0.09	0.37	0.39	0.49	0.61	0.66	0.54	0.10	0.37	0.40	0.54	0.66	0.68	<0.0005
C	1.24	0.26	0.85	0.92	1.21	1.56	1.73	1.20	0.22	0.85	0.91	1.18	1.51	1.56	N.S.
C E	3.41	0.56	2.53	2.70	3.39	4.05	4.25	3.17	0.42	2.59	2.66	3.15	3.71	3.88	<0.0005
T C	4.59	0.74	3.45	3.70	4.56	5.40	5.73	4.30	0.63	3.46	3.56	4.24	5.11	5.28	<0.0005
α-LP	1.36	0.30	0.91	0.98	1.34	1.74	1.92	1.43	0.30	0.91	1.06	1.36	1.80	1.96	N.S.
pre-β-LP	0.60	0.24	0.27	0.33	0.58	0.90	1.05	0.36	0.17	0.12	0.17	0.31	0.58	0.63	<0.0005
β-LP	2.52	0.58	1.62	1.86	2.50	3.24	3.56	2.57	0.56	1.79	1.93	2.53	3.23	3.39	N.S.
Percent distribution (%)															
α-LP	30.0	6.4	20.8	22.6	29.4	37.6	40.4	33.4	6.6	23.9	25.7	32.7	42.4	44.6	<0.0005
pre-β-LP	13.2	4.9	6.9	7.7	12.6	19.5	22.0	8.4	4.3	3.2	4.0	7.0	13.8	17.4	<0.0005
β-LP	54.8	7.8	41.9	45.7	55.1	63.0	66.0	60.0	7.1	48.0	49.6	60.6	68.5	69.9	<0.0005
Ratio															
C E : C	2.80	0.44	2.05	2.22	2.77	3.32	3.60	2.69	0.37	2.18	2.24	2.63	3.12	3.30	<0.01
T C : β-LP	1.86	0.31	1.51	1.58	1.81	2.19	2.38	1.71	0.22	1.41	1.46	1.65	2.01	2.06	<0.0005
T C : α-LP	3.49	0.82	2.46	2.65	3.39	4.42	4.75	3.11	0.61	2.24	2.34	3.03	3.87	4.09	<0.0005
β : α-LP	1.86	0.62	1.10	1.21	1.87	2.64	2.99	1.88	0.55	1.09	1.21	1.80	2.56	2.75	N.S.
P C : P E	4.77	0.79	3.60	3.89	4.69	5.75	6.00	4.26	0.73	3.21	3.35	4.14	4.97	5.87	<0.0005
P C : α-LP	1.79	0.42	1.26	1.35	1.74	2.28	2.55	1.62	0.28	1.21	1.27	1.58	2.00	2.17	<0.0005

TABLE 3

Variable	German Boys (n = 172)							German Girls (n = 163)							P
			Percentiles							Percentiles					
	$\bar{x}$	S.D.	5	10	50	90	95	$\bar{x}$	S.D.	5	10	50	90	95	
Concentration (mmol/l)															
G L U C	5.33	0.61	4.30	4.56	5.25	6.04	6.25	5.05	0.56	4.22	4.40	4.92	5.71	5.86	<0.0005
U A	0.220	0.046	0.143	0.167	0.215	0.275	0.297	0.214	0.060	0.114	0.134	0.211	0.291	0.313	N.S.
T G	0.79	0.33	0.28	0.39	0.77	1.15	1.32	0.87	0.30	0.41	0.51	0.87	1.23	1.44	<0.01
P C	2.35	0.36	1.78	1.91	2.30	2.86	2.97	2.36	0.36	1.74	1.89	2.36	2.79	2.95	N.S.
P E	0.50	0.09	0.36	0.39	0.49	0.59	0.64	0.51	0.09	0.38	0.40	0.50	0.62	0.67	N.S.
C	1.20	0.24	0.81	0.86	1.16	1.50	1.66	1.28	0.28	0.89	0.95	1.24	1.62	1.84	<0.01
C E	3.35	0.50	2.56	2.70	3.37	3.90	4.10	3.45	0.61	2.49	2.68	3.42	4.13	4.67	N.S.
T C	4.51	0.67	3.45	3.66	4.52	5.32	5.47	4.67	0.80	3.40	3.72	4.60	5.16	6.26	<0.10
α-LP	1.38	0.30	0.91	0.97	1.35	1.78	1.93	1.35	0.30	0.88	0.98	1.32	1.66	1.85	N.S.
pre-β-LP	0.61	0.24	0.26	0.33	0.58	0.93	1.04	0.60	0.24	0.27	0.32	0.57	0.90	1.04	N.S.
β-LP	2.42	0.52	1.61	1.79	2.36	3.07	3.24	2.63	0.63	1.62	1.91	2.58	3.43	3.73	<0.0005
Percent distribution (%)															
α-LP	30.7	6.2	21.7	22.7	30.4	38.3	40.8	29.3	6.6	18.5	22.4	28.8	36.0	39.0	<0.025
pre-β-LP	13.6	5.1	6.3	7.6	13.3	20.1	22.1	12.8	4.7	7.0	7.6	12.1	18.1	20.5	<0.05
β-LP	53.5	7.8	40.6	45.0	54.4	61.8	63.6	56.1	7.6	43.5	47.6	55.7	65.0	68.1	<0.0025
Ratio															
C E : C	2.86	0.46	2.15	2.31	2.82	3.42	3.66	2.75	0.42	2.03	2.18	2.73	3.26	3.49	<0.05
T C : β-LP	1.91	0.34	1.55	1.62	1.82	2.22	2.43	1.82	0.27	1.46	1.53	1.79	2.09	2.28	<0.0025
T C : α-LP	3.39	0.72	2.43	2.60	3.28	4.40	4.59	3.59	0.91	2.52	2.77	3.47	4.45	4.97	<0.025
β : α-LP	1.83	0.56	1.09	1.18	1.79	2.54	2.84	2.05	0.78	1.15	1.36	1.93	2.76	3.30	<0.005
P C : P E	4.82	0.83	3.62	3.87	4.70	5.88	6.43	4.71	0.74	3.51	3.89	4.67	5.61	5.79	N.S.
P C : α-LP	1.77	0.40	1.26	1.32	1.70	2.28	2.53	1.82	0.43	1.22	1.39	1.79	2.23	2.51	N.S.

TABLE 4

Variables	Japanese Boys (n = 49)					Japanese Girls (n = 29)					F
	$\bar{x}$	S.D.	Percentiles 10	50	90	$\bar{x}$	S.D.	Percentiles 10	50	90	
Concentration (mmol/l)											
G L U C	5.21	0.46	4.62	5.15	5.75	5.22	0.50	4.43	5.19	5.77	N.S.
U A	0.211	0.035	0.160	0.210	0.250	0.224	0.041	0.152	0.215	0.267	N.S.
T G	0.84	0.26	0.48	0.78	1.13	0.79	0.27	0.52	0.68	1.13	N.S.
P C	2.25	0.29	1.89	2.20	2.64	2.25	0.32	1.83	2.17	2.68	N.S.
P E	0.55	0.10	0.41	0.54	0.68	0.53	0.10	0.36	0.53	0.64	N.S.
C	1.18	0.20	0.92	1.17	1.48	1.24	0.24	0.87	1.21	1.56	<0.10
C E	3.16	0.35	2.73	3.15	3.64	3.20	0.52	2.59	3.10	3.86	N.S.
T C	4.22	0.52	3.56	4.20	4.86	4.45	0.78	3.55	4.40	5.23	N.S.
α-LP	1.42	0.32	1.04	1.35	1.85	1.43	0.27	1.06	1.37	1.75	N.S.
pre-β-LP	0.38	0.20	0.16	0.33	0.59	0.33	0.13	0.17	0.30	0.46	N.S.
β-LP	2.48	0.49	1.83	2.41	3.13	2.73	0.64	2.03	2.62	3.40	<0.10
Percent distribution (%)											
α-LP	33.8	7.0	25.7	33.1	42.9	32.6	5.7	23.2	32.4	39.1	N.S.
pre-β-LP	9.1	4.9	3.5	7.3	15.5	7.4	2.8	4.6	6.7	11.0	N.S.
β-LP	58.6	7.6	48.9	58.6	67.3	61.1	6.1	52.7	61.2	68.5	<0.10
Ratio											
C E : C	2.73	0.38	2.28	2.70	3.12	2.63	0.36	2.18	2.53	3.08	<0.10
T C : β-LP	1.74	0.24	1.45	1.68	2.02	1.65	0.18	1.45	1.62	1.89	<0.10
T C : α-LP	3.07	0.60	2.30	2.98	3.87	3.17	0.64	2.51	3.05	3.66	N.S.
β : α-LP	1.83	0.53	1.19	1.73	2.54	1.97	0.58	1.28	1.89	2.47	N.S.
P C : P E	4.21	0.71	3.42	4.08	4.94	4.36	0.77	3.32	4.23	5.07	N.S.
P C : α-LP	1.64	0.30	1.25	1.62	2.01	1.60	0.25	1.27	1.52	2.03	N.S.

TABLE 5

Concentration	GLUC	UA	TG	PC	PE	C	CE	TC	α-LP	pre-β-LP	β-LP
German boys vs Japanese boys	N.S.	N.S.	N.S.	<0.05	<0.0005	N.S.	<0.05	<0.0025	N.S.	<0.0005	N.S.
German girls vs Japanese girls	<0.05	N.S.	N.S.	<0.10	<0.10	N.S.	<0.025	<0.10	N.S.	<0.0005	N.S.

Percent distribution	α-LP	pre-β-LP	β-LP
German boys vs Japanese boys	< 0.01	< 0.0005	<0.0005
German girls vs Japanese girls	< 0.0025	<0.0005	<0.0005

Ratio	CE:C	TC:β-LP	TC:α-LP	β:α -LP	PC:PE	PC:α -LP
German boys vs Japanese boys	< 0.025	<0.0005	<0.01	N.S.	<0.0005	<0.05
German girls vs Japanese girls	< 0.05	<0.0005	<0.0025	N.S.	<0.005	<0.0025

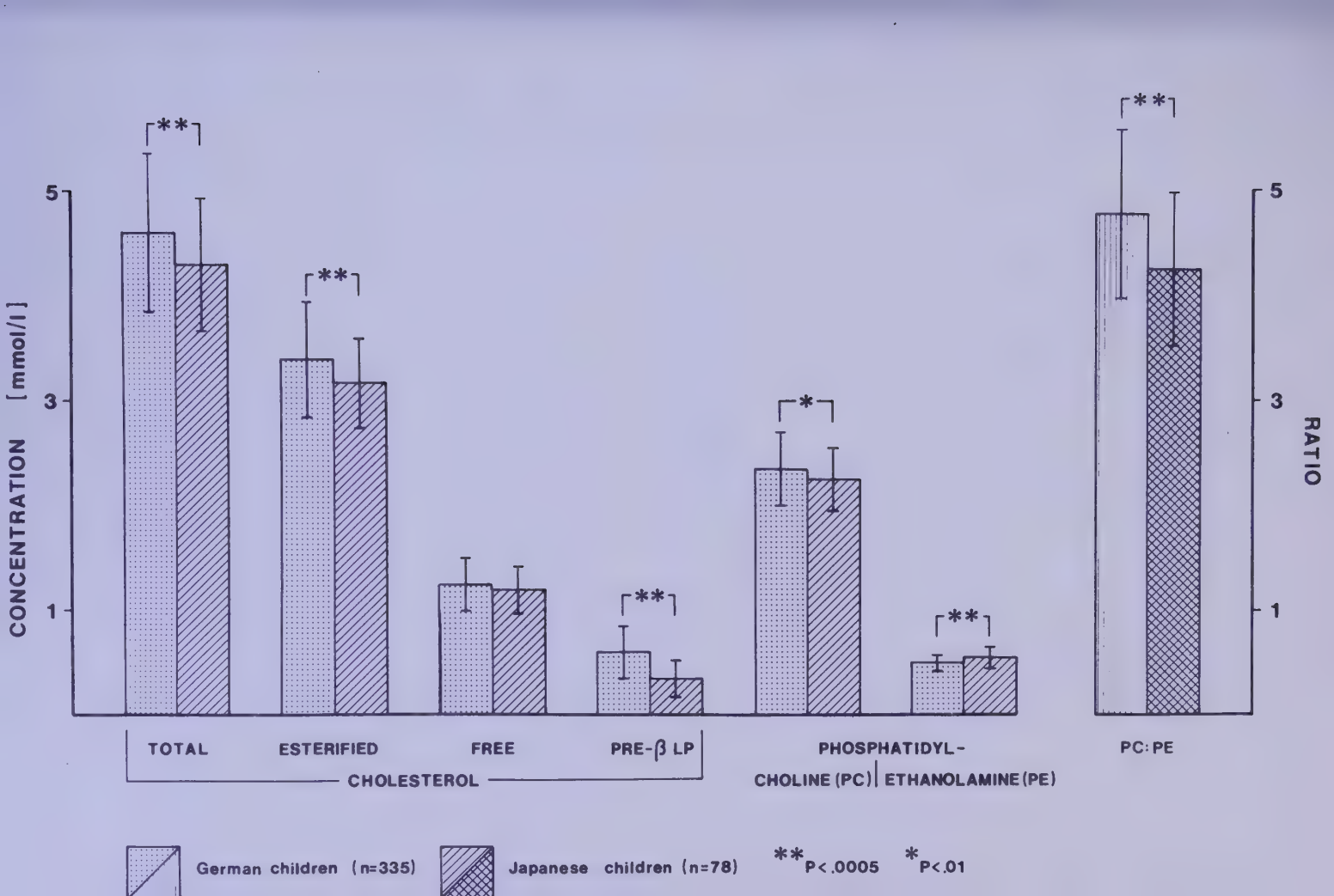
TABLE 6

	German Children			Japanese Children		
	Total	Boys	Girls	Total	Boys	Girls
T C : C	0.85(a)	0.80(a)	0.87(a)	0.75(a)	0.65(a)	0.85(a)
T C : C E	0.91 (a)	0.96(a)	0.96(a)	0.90(a)	0.84(a)	0.95(a)
C E : C	0.67(a)	0.60(a)	0.71(a)	0.71(a)	0.67(a)	0.75(a)
T C : β -LP	0.71 (a)	0.70(a)	0.82(a)	0.84(a)	0.76(a)	0.90(a)
T C : pre-β -LP	0.41(a)	0.40(a)	0.45(a)	0.10	0	0.28(f)
T C : α -LP	0.38(a)	0.48(a)	0.33(a)	0.39(a)	0.39(c)	0.44(d)
α : pre-β -LP	0	0	0	-0.34(b)	-0.43(b)	-0.10
P C : P E	0.51(a)	0.46(a)	0.56(a)	0.56(a)	0.55(a)	0.58(a)
P C : C	0.44(a)	0.42(a)	0.48(a)	0.63(a)	0.51(a)	0.80(a)
P C : C E	0.44(a)	0.47(a)	0.43(a)	0.68(a)	0.68(a)	0.70(a)
P C : β -LP	0.25(a)	0.25(d)	0.30(b)	0.46(a)	0.39(c)	0.57(b)
P C : α -LP	0.40(a)	0.32(b)	0.40(a)	0.57(a)	0.55(a)	0.63(a)
GLUC : T C	-0.10(e)	-0.13	-0.10	-0.32(b)	-0.20(f)	-0.49(c)
GLUC : C	0	0	0	-0.14	0	-0.40(a)
GLUC : C E	-0.16(d)	-0.17(e)	-0.14(f)	-0.26(c)	-0.10	-0.47(a)
GLUC : β -LP	-0.22(b)	-0.23(d)	-0.15(f)	-0.32(b)	-0.24(e)	-0.44(d)
T G : pre-β -LP	0.28(a)	0.29(b)	0.28(b)	0.45(a)	0.39(c)	0.63(a)
T G : α -LP	-0.21(b)	-0.18(e)	-0.25(c)	-0.20(e)	-0.21(f)	-0.18

No correlation : β : α -LP, β : pre-β -LP, GLUC : pre-β -LP, GLUC : α -LP, GLUC : UA, GLUC : TG, UA : β -LP.

TABLE 7

City, country (references)	Sex	Age (yr)	TG	TC	HDL α-LP	VLDL pre-β-LP	LDL β-LP	LDL/HDL	TC/HDL
Duesseldorf, Germany	Boys	3-7	0.86±0.36	4.94±0.73	1.44±0.31	0.68±0.27	2.54±0.55	1.8	3.4
(German children)	Girls	3-7	0.95±0.33	5.12±0.88	1.41±0.31	0.67±0.27	2.77±0.66	2.0	3.6
Duesseldorf	Boys	3-7	0.92±0.28	4.62±0.57	1.48±0.33	0.43±0.21	2.61±0.52	1.8	3.1
(Japanese children)	Girls	3-7	0.86±0.31	4.87±0.85	1.49±0.28	0.37±0.15	2.87±0.67	1.9	3.3
Tokyo, Japan (47)	Boys	6	-	4.15±0.57	-	-	-	-	-
	Girls	6	-	4.28±0.66	-	-	-	-	-
Geneva, Switzerland (48)	Boys	8-9	0.57	4.80±0.70	1.66±0.24	0.06	2.64±0.56	1.6	2.9
	Girls	8-9	0.60	5.06±0.80	1.61±0.33	0.08	2.72±0.61	1.9	3.1
Rochester, Minn., USA (12)	Boys	6-10	0.59±0.25	4.12±0.52	1.37±0.15	0.15±0.15	2.69±0.47	2.0	3.0
	Girls	6-10	0.65±0.29	4.15±0.62	1.30±0.21	0.21±0.15	2.77±0.47	2.1	3.2
Cincinnati, Ohio, USA (44)	Boys	6-7	0.57±0.18	4.09±0.54	1.45±0.28	-	2.44±0.54	1.7	2.8
	Girls	6-7	0.81±0.40	4.17±0.41	1.27±0.23	-	2.62±0.49	2.1	3.3
Bogalusa, Louis., USA (3)	Boys	2.5-5.5	0.72±0.30	4.01±0.62	1.56±0.47	0.16±0.16	2.28±0.53	1.5	2.5
	Girls	"	0.79±0.35	4.09±0.65	1.55±0.50	0.17±0.15	2.38±0.50	1.5	2.6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5
3
1
CONCENTRATION [mmol/l]
5
3
1
RATIO
TOTAL
ESTERIFIED
FREE
PRE-β LP
CHOLESTEROL
PHOSPHATIDYL-
CHOLINE (PC)
ETHANOLAMINE (PE)
PC:PE
German children (n=335)
Japanese children (n=78)
**P<.0005
*P<.01

Ich danke Frau Prof.Dr.I.R.Kupke
für die Themenstellung und
die Betreuung der Arbeit

L E B E N S L A U F

Ich, Friedrich-Wilhelm Ernst Wellern, wurde am 19.10.1956 als erster von zwei Söhnen des Assistenzarztes Dr. med. Paul Wellern und seiner Frau, der Assistenzärztin Dr. med. Margot Wellern, geb. Brinkmann, in Wiesbaden geboren.

Nach $3^1/_2$-jähriger Volksschulzeit von Ostern 1963 bis Herbst 1966 an der Evangelischen Volksschule I in Ratingen besuchte ich von 1966 bis 1975 das Städt. Theodor-Heuss-Gymnasium in Ratingen, wo ich am 7.6.1975 die Reifeprüfung bestand.

Zum Wintersemester 1975/76 begann ich das Medizinstudium an der Universität Düsseldorf und legte im Frühjahr 1978 die Ärztliche Vorprüfung, im Frühjahr 1979 den ersten Teil und im Frühjahr 1981 den zweiten Teil der Ärztlichen Prüfung ab. Am 29.4.1982 bestand ich an der Universität Düsseldorf die Ärztliche Prüfung und erhielt am 21.5.1982 die Approbation als Arzt.

Von August 1982 bis September 1983 war ich als Assistenzarzt an der Medizinischen Klinik des Klinikums Barmen in Wuppertal tätig. Seit Oktober 1983 bin ich als Assistenzarzt an der Universitäts-Augenklinik der Gesamthochschule Essen tätig, um mich zum Arzt für Augenheilkunde ausbilden zu lassen.

Friedrich Wellern